J Neurol Disord
Volume 10:8, 2022

Journal of Neurological Disorders

Research Article

Open Access

# An Analysis of Global Research Hotspots and Trends on Gut Brain Axis with Web-Based Scientific Database

**Wei Ma[1], Yi-Bao Yang[2], Ting-Ting Xie[3], Zhi-Ying Gong[1] and Xue-Ni Mo[1*]**

[1]*Department of Medicine, Guangxi University of Chinese Medicine, China*
[2]*Department of Medicine, Ruikang Hospital Affiliated of Guangxi University of Chinese Medicine, China*
[3]*Department of Medicine, The First Affiliated Hospital of Guangxi University of Traditional Chinese Medicine, China*

## Abstract

**Background:** Since it was first mentioned in the early 200 century, the brain gut axis, a bidirectional pathway mediating between the gastrointestinal system and the central nervous system (CNS), has attracted increasing attention and has been found to play an important role in the treatment of certain diseases. Our study aims to analyze the scientific results of the brain gut axis research and identify the major research hotspots and frontier areas of the brain gut axis.

**Materials and methods:** Publications focusing on the brain gut axis were retrieved from the Web of Science core collection database and screened according to the inclusion criteria. Citespace5.8.R3 and Microsoft Excel 2019 were used to evaluate and visualize the results, including the generation of web maps and the analysis of annual publications, countries, categories, bibliographic and co-cited references, and keywords, etc. The retrieval time of the article was from January 1st, 2012 to March 31st, 2022.

**Results:** A total of 2309 original articles related to the brain gut axis were retrieved, and the overall number of those articles showed a rapid rising trend. According to our research results, the articles published by Clarke and G in 2013 are the most symbolic references in the field of brain gut axis, with the highest citation rate (910 times). Nutrition is the most active Journal (81 articles) and the most published articles are in the United States (661 articles). We also observed that the leading institutions are Univ coll cork (82 articles) and cryan JF, John cryan, Dinan TG, which have made outstanding contributions in this field. Additionally, the most common keywords are the gut and most of the mechanisms of the gut, the role of microorganisms in the gut flora brain axis and their application in intestinal syndrome.

**Conclusion:** With increasing evidence on the role of the brain gut axis in IBS and other diseases, application of the brain gut axis has gradually become a new research hotspot in clinical treatment, which deserves further research.

**Keywords:** Gut brain axis • Citespace • Bibliometrics • Irritable bowel syndrome • Exposure

## Introduction

The concept of the brain gut axis was developed by Mike, a neurologist at the University of Georgia, in the early 20th century. Professor Gelsong first proposed, refers to the two way pathway formed between the central nervous system and the intestinal nervous system, which represents the two way relationship between brain and intestinal regulation of gastrointestinal function [1]. The brain gut axis mainly includes CNS, intestinal nervous system, autonomic nervous system; hypothalamus pituitary kidney upper gland intestinal flora can affect nerve and gastrointestinal function through a variety of ways. Gut microbiota affects host activities like stress, immunity, anxiety and depression through the gut brain axis, participates in the pathophysiology of various diseases, such as diabetes, obesity and neurological diseases, and has many potential molecular therapeutic targets [2,3].

In recent years, the brain gut axis has received more attention in various research fields, and many academic journals have published articles on the brain gut axis research, but few researches has systematically investigated the scientific achievements and current situation of the field from a global perspective. Therefore, it is necessary to apply visual analysis to reveal the global status, future research trends and hotspots of brain gut axis research.

Bibliometry takes the global literature pattern and literature characteristics as the research object, and uses mathematics, statistics and other methods to study the distribution pattern, quantitative relationship and change law of literature information, and then explore the structure, characteristics and law of science and technology. Bibliometry can not only allow quantitative and statistical analysis of domain specific publications but also accurately reveal the most representative studies [4]. In addition, the results of bibliometric analysis can be presented with massive data in the form of a knowledge graph, and researchers can comprehensively analyze the development of a discipline and intuitively understand the frontier trends [5]. Therefore, this paper uses Bibliometrics method to statistically analyze the domestic and foreign literatures related to brain gut axis, and uses Citespace 5.8 R3 and vosviewer software visualize the statistical results, which are used to summarize the research progress and hot spots of brain gut axis, help scholars quickly understand the current situation and hot spots of brain gut axis and formulate research strategies, and provide literature data support for the mechanism research of brain gut axis and the development of drugs targeting brain gut axis [6,7].

## Materials and Methods

### Source of database and data collection

We applied the Web of Science Core Collection (WoSCC) as the source of database for data retrieval. The WoS Core Collection is a canonical online database, providing standardized and up to date reference datasets for scientific research and analysis. The retrieval time of all articles was determined from January 1st, 2012 to March 31st, 2022. In the web of

***Address for Correspondence:** Xue-Ni Mo, Department of Medicine, Guangxi University of Chinese Medicine, China, Email: 539892598@qq.com*



**Received:** 01-August-2022, Manuscript No. jnd-22-71742; **Editor assigned:** 3-August-2022, PreQC No. P-71742(PQ); **Reviewed:** 7-August-2022; QC No. Q-71742; **Revised:** 22-August-2022, Manuscript No. R-71742; **Published:** 29-August-2022, **DOI:** 10.4172/2329-6895.10.8.508

Science Core Collection (WOS) database, the set retrieval formula was constructed of theme (brain gut axis OR gut brain axis) and language (English); the retrieval results were de duplicated, and non-representative entries such as conference contributions, news, corrigenda, etc. were deleted [8]. Finally, 2309 documents were screened out in the web of science database. For document types, only articles were included in this study, and all other document types were excluded. Nevertheless, in order to ensure the quality of the search, two independent authors participated in the search process to perform and confirm the search queries and results. The number of publications on the brain gut axis increased rapidly in 2022, which led us to include new articles published in 2022. However, since we did not include the literature in the last nine months of 2022 when setting the time span, the data in 2022 is not complete, and the analysis of this study does not represent the whole year. However, it does give us a further understanding of the latest research trends in the field of brain gut axis, which will be learned in the research background. The research flow chart is shown in Figure 1.

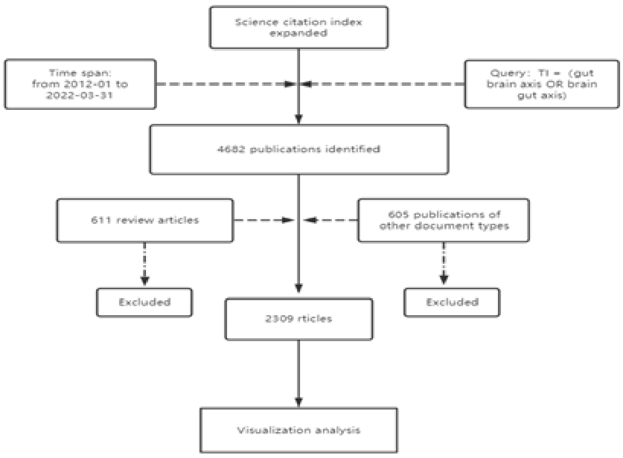


**Figure 1.** Research flow chart of search strategies and selection processes for publications related to the brain-gut axis.

### Parameters setting and data analysis

By putting the retrieved data into citespace5.8 In R3 software, a visual map was generated to analyze the annual output, countries, highly cited documents, keywords and burst detection. In addition, Visual Co citation and co citation were used to study the cooperative relationship between the identified publications [9]. The parameter settings of Citespace5.8.R3 were as follows: years per slice from January 1st, 2012 to March 31st, 2022, years per slice (1), links (strength=cosine; scope=within slices); selection criteria (g-index, k=25), pruning (pathfifinder+pruning sliced network) □ words of "author", "keyword", "institution", "country", "reference", "cited author", "cited journal" for node types; selection criteria (g-index k=25). The software Microsoft office Excel 2019 and Citespace5.8.R3 were applied to carry out data analysis, and Microsoft Office Excel 2019 management database to analyze the annual publication output and trend of brain gut axis publications [10].

The Java program VOS Viewer is used to build the network visualization maps [11]. It is a commonly used software tool for scientific literature mapping and clustering based on bibliometric data. In this study, the software was used for institutional citation and keyword co-occurrence. In the VOS viewer diagram, each node represents a different parameter, such as a mechanism or keyword. The size of nodes is determined by the weights of parameters, such as number of publications, citations or frequency. The higher the weights, the larger the nodes. Nodes and lines are colored by the cluster where they belong. Lines between the nodes indicate the links. Link strength is assessed by the Total Link Strength Index (TLS) and can be extended to reflect link strength between institutions or keywords.

Citespace5.8.R3 is used to visualize data and analyze trends and patterns in the identified scientific literature, as well as to explore research hotspots, research frontiers, key research topics, and key authors, institutions, and countries, while helping to predict the future direction of a certain field of research. The analysis of the methods includes co-occurrence, clustering, and burst. The visual chart types include histograms, cluster views, and collinearity. All clusters are marked with keywords and use the log likelihood rate (LLR) as the clustering algorithm [12,13]. In the resulting analysis graph, the synonyms were combined according to the actual situation

## Results

### Annual publications

A total of 2309 relevant publications were collected by searching the subject words. Figure 2 shows the frequency distribution of selected articles consistent with the year of publication. From 2021 to 2022, the number of publications applicable to each year increases year by year. The number of published papers on the brain gut axis can be divided into three stages. The first stage is from 2012 to 2015, and the number of publications increases steadily. The second stage is from 2016 to 2017, and the output of publications gradually increases. The last stage is from 2018 to 2022, and the number of publications increases significantly. According to the software, the frequency of documents issued in 2022 has tripled compared with that in 2018. Although the relevant data in 2022 are not yet complete, it is expected that the final number of documents issued in 2022 will rise rapidly.

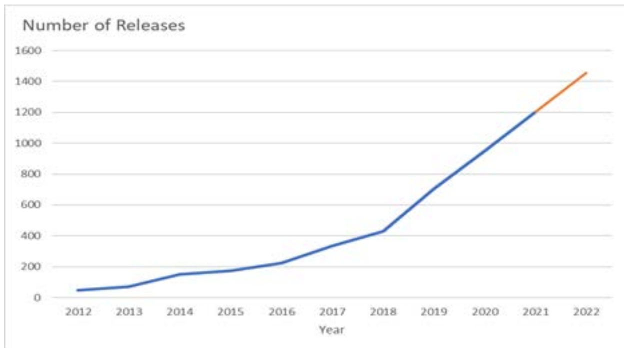


**Figure 2.** Annual frequency of publications in the brain-gut axis field.

### Sources of funds

The top ten major fund sources are shown in Table 1 National Natural Science Foundation of China NSFC, National Institutes of Health NIH Usa and United States Department of Health Human Services mainly supports this area, China, USA, and European Union provided the most help in the field.

**Table 1.** Top 10 Funding Sources in the gut brain axis Field.

| Rank | Fund source | Country/Region | Frequency |
|---|---|---|---|
| 1 | National Natural Science Foundation Of China NSFC | China | 395 |
| 2 | National Institutes Of Health NIH Usa | Usa | 322 |
| 3 | United States Department Of Health Human Services | Usa | 322 |

| | | | |
|---|---|---|---|
| 4 | European Commission | European Union | 177 |
| 5 | Science Foundation Ireland | Ireland | 77 |
| 6 | NIH National Institute Of Diabetes Digestive Kidney Diseases Niddk | Usa | 76 |
| 7 | German Research Foundation DFG | Germany | 57 |
| 8 | Ministry Of Education Culture Sports Science And Technology Japan Mext | Japan | 51 |
| 9 | UK Research Innovation Ukri | England | 45 |
| 10 | Canadian Institutes Of Health Research Cihr | Canada | 41 |

## Countries/regions, institutions, authors, and collaborative analysis

2309 articles have been published by research groups from 53 countries. Figure 3 shows the distribution of different countries or regions conducting brain gut axis research. Here we list the top 10 countries in the research of brain gut axis, including 6 European countries, 2 Asian countries and 2 North American countries. USA is the country with the most published articles (661), accounting for nearly 1/3 of the total, surpassing China (630) and Italy (145), followed by Canada (139) and Germany (135) (Table 2). Figure 4 shows the cooperative relationship between countries/regions. China attaches great importance to cooperation and has a very close relationship with the United States.

**Table 2.** Top 10 countries and institutions with the largest number of publications on the brain-gut axis.

| Rank | Country | Frequency | Total citations | Citation per year | Rank | Institution | Frequency | Country |
|---|---|---|---|---|---|---|---|---|
| 1 | USA | 661 | 18137 | 26.13 | 1 | Univ Coll Cork | 82 | Ireland |
| 2 | China | 630 | 10299 | 15.91 | 2 | McMaster Univ | 41 | Canada |
| 3 | Italy | 145 | 2745 | 18.67 | 3 | Chongqing Med Univ | 40 | China |
| 4 | Canada | 139 | 4672 | 32 | 4 | Chinese Acad Sci | 38 | China |
| 5 | Germany | 135 | 2838 | 19.57 | 5 | Univ Calif Los Angeles | 35 | Usa |
| 6 | Ireland | 111 | 7857 | 68.92 | 6 | Univ Gothenburg | 26 | Sweden |
| 7 | France | 105 | 3153 | 24.83 | 7 | Univ Toronto | 24 | Canada |
| 8 | England | 102 | 2941 | 25.8 | 8 | Zhejiang Univ | 23 | China |
| 9 | Japan | 102 | 2053 | 18.66 | 9 | CNR | 22 | Usa |
| 10 | Spain | 95 | 1744 | 17.27 | 10 | Chiba Univ | 22 | Japan |

The institutions with the top 3 articles on brain gut axis are Univ coll cork in Ireland (82 articles), McMaster Univ in Canada (41 articles) and Chong Qing Med Univ in China (40 articles) (Table 2); The institutional cooperation chart shows that there is cooperation between Univ coll cork, McMaster Univ, CNR, Teagasc food res CTR and Natl Univ Ireland Univ coll cork, between Chong Qing Med Univ, Zhejiang Univ, capital Med Univ and Jin Univ, and between Chinese Acad SCI, Univ Chinese Acad SCI, Chengdu Univ traditional Chinese Med and Sichuan Univ, as shown in Figure 5.

**Figure 3.** Country / regional distribution of the brain-gut axis field.

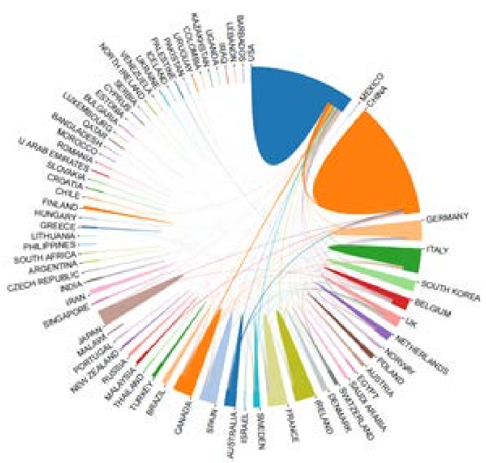

**Figure 4.** The cross-country collaborations visualization map.

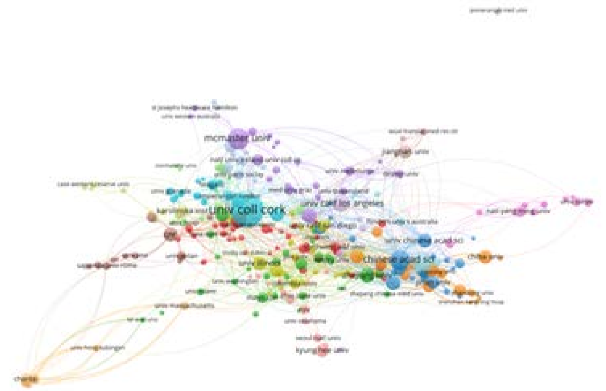


**Figure 5.** Institutional cooperation diagram.

The top three authors in the field of brain gut axis are cryan JF (80 articles), John cryan (73 articles) and Dinan TG (67 articles). The top three authors cited most frequently are cryan J (498 times), Dinan t (383 times) and Mayer e (354 times). The top 10 authors of the brain gut axis in the web of science database are shown in Table 3. They are the most influential authors in the field of brain gut axis research.

**Table 3.** Top 10 authors of brain axis publication volume and citation frequency.

| Rank | Author | Frequency |
|---|---|---|
| 1 | Cryan JF | 80 |
| 2 | John Cryan | 73 |
| 3 | Dinan TG | 67 |
| 4 | Timothy Dinan | 59 |
| 5 | Clarke Gerard | 28 |
| 6 | Gerard Clarke | 28 |
| 7 | Catherine Stanton | 27 |
| 8 | Stanton Catherine | 22 |
| 9 | Xie Peng | 18 |
| 10 | Kenji Hashimoto | 18 |

## Journal analysis

In the web of science database, there are 231 brain gut axis literatures published in three top level journals, "nutrients", "scientific reports" and "brain behavior and immunity", accounting for 9.4% (231/2309). Articles on brain gut axis have been published in different journals, and only the top ten journals with published papers are listed here. Among them, there are 7 journals in JCR zone 2, 3 journals in zone 3, and 6 journals with impact factor (if) >12 (Table 4). Journals, where only the top ten journals are published, including 7 journals in JCR in zone 2,3 journals in zone 3, and 6 journals with influence factor (IF)>12 points, as shown in Table 4.

## References and co-references

References: A total of 2309 documents were cited 54441 times, with an average of 22.24 times per paper, and the h-index was 103. It is arranged in descending order in Table 5. The two literatures cited more than 800 times are published by Clarke, G, and scheperjans, F. they name and establish that the brain gut axis is a new way in neuroscience. Clarke, G. et al. Published an article entitled "the microbiome gut brain axis during early life regulations the hippocampal serotonergic system in a sex dependent manner", which is the article with the most citations, with a total of 910 citations and an average of 91 citations per year. Following Clarke's research, scheperjans was cited 838 times in 2015, with an average of 104.75 citations per year, and Zheng, The research published by P is entitled "gut microbiome remodeling inducing passive like behaviors through a path mediated by the host's metabolism", which has been cited 771 times, with an average of 110.14 times per year. The first six articles were published in the journals molecular psychiatry, movement disorders, molecular psychiatry, Journal of psychological research, nature and nature microbiology.

**Table 4.** Journals with 20 articles on the brain-gut axis.

| Rank | Journal | Frequency | Impact factor | JCR partition | Total citations |
|---|---|---|---|---|---|
| 1 | Nutrients | 81 | 8.1 | 2 | 657 |
| 2 | Scientific Reports | 78 | 26.44 | 2 | 2062 |
| 3 | Brain Behavior And Immunity | 72 | 45.07 | 2 | 3245 |
| 4 | Plos One | 45 | 37.02 | 2 | 1666 |
| 5 | Neurogastroenterology And Motility | 37 | 38.16 | 3 | 1412 |
| 6 | Psychoneuroendocrinology | 30 | 51.33 | 2 | 1540 |
| 7 | Frontiers In Neuroscience | 29 | 12.72 | 3 | 369 |
| 8 | Frontiers In Cellular And Infection Microbiology | 25 | 9.36 | 2 | 234 |
| 9 | Frontiers In Psychiatry | 23 | 8.39 | 3 | 193 |
| 10 | International Journal Of Molecular Sciences | 23 | 6.87 | 2 | 158 |

**Table 5.** Literature on the brain-gut axis cited for more than 350 times.

| Rank | References | Journal | Total citations | Citation per year |
|---|---|---|---|---|
| 1 | Clarke, G (2013) | Molecular Psychiatry | 910 | 91 |
| 2 | Scheperjans, F (2015) | Movement Disorders | 838 | 104.75 |
| 3 | Zheng, P (2016) | Molecular Psychiatry | 771 | 110.14 |
| 4 | Kelly, JR (2016) | Journal Of Psychiatric Research | 616 | 88 |

| | | | | |
|---|---|---|---|---|
| 5 | Perry, RJ (2016) | Nature | 597 | 85.29 |
| 6 | Valles-Colomer, M (2019) | Nature Microbiology | 533 | 133.25 |
| 7 | Mayer, EA (2014) | Journal Of Neuroscience | 443 | 49.22 |
| 8 | Benakis, C (2016) | Nature Medicine | 418 | 59.71 |
| 9 | Leclercq, S (2014) | Proceedings Of The National Academy Of Sciences Of The United States Of America | 416 | 46.22 |
| 10 | Burokas, A (2017) | Biological Psychiatry | 367 | 61.17 |
| 11 | South, AM (2020) | American Journal Of Physiology-Heart And Circulatory Physiology | 360 | 120 |
| 12 | Desbonnet, L (2015) | Brain Behavior And Immunity | 355 | 44.38 |

Co-references: Co citation analysis can help researchers find a common knowledge base in many studies efficiently and conveniently. We input 2309 retrieved articles into Citespace5.8.R3 software, a co citation analysis was carried out. After setting parameters, a visual co citation diagram of the identified literature was generated. Table 6 lists the top 8 co citation references in terms of co citation frequency. The most cited reference is Zheng, P is equal to "gut microbiome remodeling inducing negative like behaviors through a path mediated by the host's metabolism" published in 2016, and the number of citations is 122. Followed by cryan, JF, 2019 and Jiang, hy, 2015, which have been cited 118 times and 117 times respectively.

**Table 6.** Brain-gut axis literature of the top 8 cited frequencies.

| Rank | References | Journal | Co-citation |
|---|---|---|---|
| 1 | Zheng, P (2016) | Molecular Psychiatry | 122 |
| 2 | Cryan, JF (2019) | Physiological Reviews | 118 |
| 3 | Jiang, HY (2015) | Brain Behavior And Immunity | 117 |
| 4 | Sampson, TR (2016) | Cell | 114 |
| 5 | Cryan, JF (2012) | Nature Reviews Neuroscience | 98 |
| 6 | Kelly, JR (2016) | Journal Of Psychiatric Research | 98 |
| 7 | Burokas, A (2017) | Biological Psychiatry | 86 |
| 8 | Valles-Colomer, (2019) | Nature Microbiology | 86 |

We also constructed a visual map to cluster the commonly cited references with the help of Citespace5.8.R3 clustering function. The retrieved literatures were divided into 8 clusters by cluster analysis. The literatures in each cluster were closely related to each other and coordinate with each other in specific fields [14,15]. The results of visual analysis were displayed in the form of knowledge map. Generally speaking, Q>0.3 means that the clustering structure is significant; When the average contour value of clustering S value is greater than 0.5, clustering is generally considered to be reasonable. If S value is greater than 0.7, the clustering result is considered to be convincing. The modular Q value is 0.4269, while the average contour value S value is 0.6795, indicating that the clustering structure is stable and highly persuasive. It is worth noting that the Q/S value of the co citation analysis is even higher than that of the coauthor analysis. Clustering nomenclature reflects the cutting edge research in a certain field. In this research, clustering was automatically generated and marked by log likelihood ratio (LLR) algorithm [16].

## Research on hot spots and key topics

Co-occurrence analysis: Keywords are the core content of the document, and Citespace5.8.R3 software was used to generate the keyword co-occurrence diagram of brain gut axis, as shown in Figure 6. As a result, the time span is from January 1st, 2012 to March 31st, 2022, the node is 557, the connection is 2209, and the density value is 0.0143. Nodes represent keywords. The larger the circle is, the higher the frequencies of keywords are. Each circle is composed of a number of concentric color rings. The color of the ring represents the publication time of the literature containing the corresponding keywords, and the width of the ring represents the number of published literature in this time unit. The thickness of links between nodes indicates the frequency of two keywords in the literature, that is, the degree of relevance. After combining synonyms and similar keywords, the 10 keywords with the highest frequency are intestinal microbiota (624 times), brain gut axis (440 times), brain (330 times), irritable bowel syndrome (252 times), stress (233 times), behavior (224 times), microbiota (221 times), expression (219 times), inflammation (214 times), and anxiety (194 times) (Table 7). It can be inferred that the study of brain gut axis involves not only the manifestations and possible mechanisms of intestinal microbiota and inflammation, but also the exploration of diseases such as irritable bowel syndrome and anxiety disorder. In addition, the intestinal microbiota in the brain gut axis is widely involved in the occurrence and development of neurodegenerative diseases, cancer and other diseases [17,18].

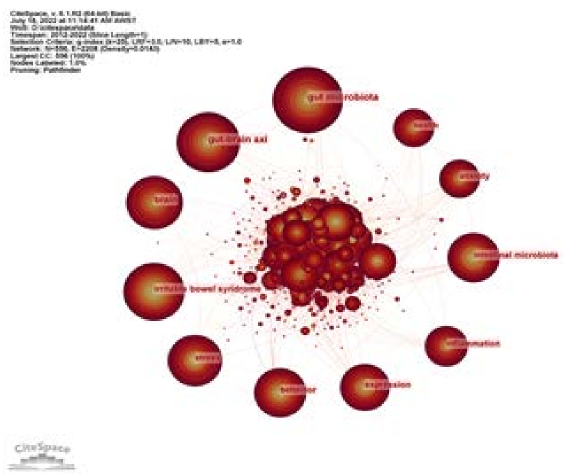

**Figure 6.** Keywords co-occurrence in the brain-gut axis study.

**Table 7.** High-frequency keywords in brain-gut axis study (170 words frequency).

| Rank | Keywords | Frequency | Begin |
|---|---|---|---|
| 1 | Gut microbiota | 624 | 2013 |
| 2 | Gut-brain axis | 440 | 2012 |
| 3 | Brain | 336 | 2013 |

| | | | |
|---|---|---|---|
| 4 | Irritable bowel syndrome | 252 | 2012 |
| 5 | Stress | 233 | 2012 |
| 6 | Behavior | 224 | 2012 |
| 7 | Expression | 219 | 2013 |
| 8 | Inflammation | 214 | 2014 |
| 9 | Anxiety | 194 | 2013 |
| 10 | Health | 179 | 2015 |

Cluster analysis: Cluster analysis can show the knowledge structure of a certain field. Clustering the keywords contained and summarizing the topics of each cluster can help researchers understand the hot spots and ongoing trends of brain gut axis research. According to the link strength of co-occurrence terms [19], the network is divided into 11 clusters# 0 is related to obesity, \1 is mainly related to gastrointestinal morbidity and treatment intervention, \2 is related to autism spectrum disorder; epithelial barrier; And \3 are related to major depressive disorder, Alzheimer's disease, neuroinflammation and other diseases, \4 including short chain fatty acids, immune system and other fields# It mainly involves the nervous system, cognitive impairment, oxidative stress and other issues# 6 including anorexia nervosa; gut microbiome; extrinsic innervation; Etc# 7 including fine motricity; sex differences; Exposure, etc. (Figure 7 and Table 8).

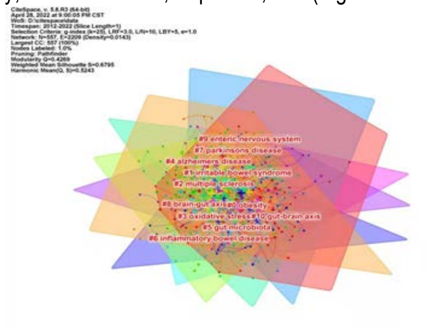


**Figure 7.** Cluster view of the brain-gut axis study.

**Table 8.** Keyword clustering list.

| Cluster ID | Size | Silhouette | Mean (Year) | Top Terms(LSI) |
|---|---|---|---|---|
| #0 | 72 | 0.618 | 2016 | eating disorder; dietary lipid; food reward; eating behavior \| gut microbiota; ferulic acid; exendin-4; anxiety; obesity (115.88, 1.0E-4); food intake (93.19, 1.0E-4); satiety (37.28, 1.0E-4); body weight (33.19, 1.0E-4); bariatric surgery (27.95, 1.0E-4) |
| #1 | 66 | 0.767 | 2015 | irritable bowel syndrome; functional dyspepsia; brain; system; metaanalysis \| gut-brain axis; gut microbiota; Alzheimer's disease; lactobacillus plantarum; cognitive dysfunction; irritable bowel syndrome (167.82, 1.0E-4); functional dyspepsia (52.49, 1.0E-4); visceral hypersensitivity (41.81, 1.0E-4); gut microbiota (36.31, 1.0E-4); abdominal pain (28.56, 1.0E-4) |
| #2 | 63 | 0.649 | 2016 | autism spectrum disorder; epithelial barrier; alcohol addiction \| gut brain axis; gut microbiota; gene-environment interactions; single nucleotide polymorphisms; peptidoglycan recognition protein; gut brain axis (36.9, 1.0E-4); s disease (20.74, 1.0E-4); cell (20.69, 1.0E-4); 16s rrna (18.01, 1.0E-4); |
| #3 | 62 | 0.589 | 2017 | gut-brain axis; high fat diet; transcription factor; animal models \| gut microbiota; Alzheimer's disease; outer membrane vesicles; nuclear factor kappa b; interleukin-1 beta; gut microbiome (34.39, 1.0E-4); systemic inflammation (30.77, 1.0E-4); major depressive disorder (29.01, 1.0E-4); pregnancy (20.5, 1.0E-4); neuroinflammation (17.59, 1.0E-4) |
| #4 | 57 | 0.622 | 2018 | ingestible sensor; viral shunt; maternal microbial inheritance; microbial sentinel cells \| gut microbiota; pineal gland; animal models; pain-related fear; tissue damage; gut microbiota (79.37, 1.0E-4); gut-brain axis (58.55, 1.0E-4); short-chain fatty acids (30.36, 1.0E-4); irritable bowel syndrome (22.81, 1.0E-4); immune system (19.48, 1.0E-4) |
| #5 | 52 | 0.692 | 2015 | gut-brain axis; gut microbiota; Alzheimer's disease; fecal microbiota transplantation; dietary fiber \| oxidative stress; doca-salt model; visceral afferents; neuronal tract-tracers; small intestine; fecal microbiota transplantation (39.01, 1.0E-4); Alzheimer's disease (38.32, 1.0E-4); cognitive impairment (34.91, 1.0E-4); gut dysbiosis (34, 1.0E-4); oxidative stress (27.02, 1.0E-4) |
| #6 | 43 | 0.622 | 2018 | anorexia nervosa; gut microbiome; extrinsic innervation; parabacteroides distasonis \| gut microbiota; brain; fermentation; hindgut; horse; gastrointestinal microbiome (18.61, 1.0E-4); 16s rrna sequencing (14.54, 0.001); microbiome-gut-brain axis (14.53, 0.001); fermentation (11.5, 0.001); anti-inflammatory effects (11.5, 0.001) |
| #7 | 39 | 0.742 | 2017 | fine motricity; sex differences; prefrontal cortex; concurrent exposure \| gut microbiota; autism spectrum disorders; abdominal pain; oral microbiota; co-occurring conditions; health (33.16, 1.0E-4); impact (32.43, 1.0E-4); exposure (20.71, 1.0E-4); autism spectrum disorder (20.56, 1.0E-4); diversity (16.4, 1.0E-4) |

Burst detection: Burst detection of keywords refers to the detection of keywords that occur frequently in a certain period of time, which helps researchers analyze the evolution of brain gut axis research [20]. In this paper, the time period is set from January 1st, 2012 to March 31st, 2022, including irritable bowel syndrome, brain gut axis, intestinal microbiota, food intake, anxiety like behavior, functional dyspepsia, visceral pain, etc. Generally speaking, irritable bowel syndrome has the strongest outbreak intensity (intensity=31.85), followed by brain gut axis (intensity=17.58) and intestinal microbiota (intensity=17.31). Since Professor Mike Gersson, a neuroscientist at the University of Columbia in the United States, put forward the concept of brain gut axis, brain gut axis has attracted more and more attention of researchers. From 2014 to 2017, intestinal microbiota (intensity=17.31) was considered to be an important factor in brain gut axis. In the short term from 2015 to 2016, visceral pain (intensity=7.35) broke out. In recent years, exposure (intensity=4.75) has become the latest explosion. From 2020 to now, it shows that this is the latest research hotspot, and this situation may continue to exist in the near future (Figure 8).

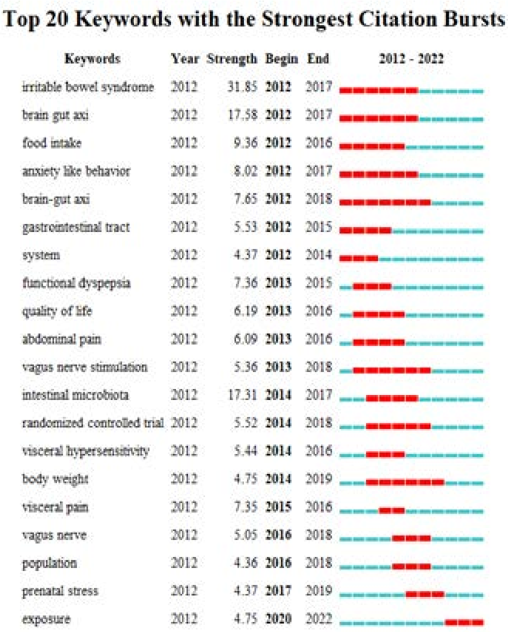


**Figure 8.** Outburst map of keywords related to the brain-gut axis.

# Discussion

## Number of articles

Since 2012, according to the number of articles published, it has been divided into three stages. In the first and second stages, the annual output of the literature on the brain gut axis has increased steadily, indicating that the number of people paying attention to this field has gradually increased. The rapid growth in the third stage indicates that the importance of research is increasingly recognized. In addition, the papers published since 2019 account for about 68% of all the extracted literatures, which indicates that the brain gut axis has gradually attracted the attention of scholars in recent years. Therefore, the brain gut axis may still be a hot topic, and the number of publications is expected to continue to increase in the next few years.

Among the top 10 countries and institutions in the research of brain gut axis in the web of science database, only 2 have published more than 600 articles in these 10 countries and regions. However, the earliest research on the brain gut axis was first proposed by Professor Michael Gelsson, a neuroscientist at the University of Columbia in the United States. He carried out relevant research earlier than scholars in other parts of the world. Therefore, the United States is one of the main driving forces for the academic reputation of brain gut axis research. China is the only developing country among the top five producing countries. At present, China's publishing volume is growing rapidly, second only to the United States, ranking second in the world.

## References and Co-references analysis

Highly cited references are classic literatures, mainly involving the mechanisms and potential pathways of the brain gut axis. However, with further research, new research on the regulation and manipulation of the brain gut axis in human diseases has gradually increased in this field. The two literatures cited more than 800 times are those published by Clarke, G, etc. and scheperjans, F, etc., naming and establishing that the brain gut axis is a new research method in neuroscience [21]. Cryan. JF and others have found that many diseases such as anxiety disorder, Parkinson's disease and Alzheimer's disease involve intestinal microbiota. Future research will focus on understanding the mechanism of microbiota brain gut axis, and try to clarify the intervention and treatment strategies of neuropsychiatric diseases based on microorganisms [22]. Valles Colomer m and others found microorganisms γ-The potential role of aminobutyric acid production in depression provides population scale evidence for the connection between microbiome and mental health, and emphasizes the importance of confounding factors [23]. Dalile B et al. Found that short chain fatty acids (SCFAs) play a key role in microbiota brain gut crosstalk, and promoted the future direction of direct investigation of the impact of SCFAs on psychological function [24]. Zheng, P et al. (2016), Kelly, Jr et al. (2016), burokas, a et al. (2017) and Valles Colorer, m et al. (2019) all appear in Tables 6 and 7, suggesting that these four documents are highly central and recognized classics in the field of brain gut axis.

## Keyword analysis

According to the existing research, the brain gut is the bidirectional pathway between the gastrointestinal system and the central nervous system, involving nerve, endocrine, immune. Information is transmitted from the intestine to the brain through vagus nerve and spinal cord afferent neurons, immune mediators such as cytokines, brain gut peptides and intestinal microbiota signal molecules, and the brain will also respond to receive information to maintain balance [25-27]. The brain gut axis contributes to many organ injuries and neurodegenerative diseases [28,29]. The most common types of organ damage are gastrointestinal injury and brain injury. It also illustrates the role of brain gut axis in neurodegenerative diseases during aging, including Parkinson's disease, Alzheimer's disease, multiple sclerosis, etc. [30-32], but it is also related to anxiety and depression like diseases. Most diseases affecting the human system involve brain gut axis to a certain extent [33,34].

The brain gut axis is an important network for communication through many pathways, such as between the vagus nerve and the ENS [35]. After the onset of brain gut axis, the brain gut axis can be significantly troubled by damps induced by injury, cytokine release, blood brain barrier (BBB) changes, microbiota changes or ecological disorders, and intestinal leakage, resulting in the migration of inflammatory and immune cells from the intestine to the brain [36-38]. Researchers found that the main pathological feature of Parkinson's disease is the loss and abnormality of dopaminergic neurons in the substantia nigra α-Synuclein aggregation [39,40]. More and more evidence shows that brain gut axis plays an important role in the pathogenesis of Parkinson's disease. Irritable bowel syndrome (IBS) is one of the most common chronic functional gastrointestinal diseases. Researchers found that brain gut axis plays an important role in the pathophysiological process of IBS, and visceral hypersensitivity is one of the hallmarks of IBS [41,42]. Although the exact cause of IBS is still unknown, studies have shown that there are a variety of complex factors that interact to lead to the onset and deterioration of the disease [43,44]. The study found that rifaximin is a broad spectrum antibiotic, which can be used as a reference treatment for irritable bowel syndrome [45]. In terms of mechanism, the anti-inflammatory effect of rifaximin and the activation of PXR attenuated nuclear factor kB (NF-KB) signal transduction and reduced the expression of proinflammatory cytokines (IL-10, IL-1 ß, TNF-a). Rifaximin changed the intestinal microbial community, prevented mucosal inflammation, improved the barrier function of the small intestine, and reduced visceral hyperalgesia [46,47]. In conclusion, although the exact mechanism of rifaximin has not been fully elucidated, the disorder in the intestinal flora is sensitive to the effect of rifaximin on short term treatment [48,49].

In general, clarifying the role of brain gut axis in the pathogenesis and treatment of irritable bowel syndrome has become a new research hotspot in recent years [50]. In addition, more and more evidence shows that there is a potential correlation between brain gut axis related genes and human diseases, especially gastrointestinal diseases. The brain gut axis has shown great prognostic and diagnostic value in a variety of diseases, such as ischemic stroke, Alzheimer's disease, depression and so on [51-54]. However, despite its clinical value, the exact molecular mechanism of brain gut axis affecting other diseases is still unclear, and further research is still needed.

The results of the outbreak map show that exposure and prenatal stress are the latest outbreak terms in recent years, indicating that these are the current research hotspots in this field [55]. In recent years, the research on brain gut axis has expanded to all aspects, and many studies have been published in well-known journals [56,57]. Environmental exposure from microorganisms to exotic organisms and even social psychology is helping to fill this explanation gap through correlation research, and is increasingly recognized as a potential trigger. More and more evidence shows that environmental exposure plays an important role in the pathogenesis of many neuropsychiatric diseases, and its potential mechanism may be complex, involving the development sensitive interaction of genetic/epigenetic, detoxification and immune factors [58,59]. In addition, the intestinal microbiome (which affects intestinal and blood brain barrier permeability through the potential biological mechanisms of vagus nerve, neuroactive peptides and factors) has been identified as exogenous exposure and inflammatory pathways and neuropsychiatric results. In the process of class may be exposed to different types of radiation, usually in the form of low linear energy transfer (let) radiation, such as for cancer treatment. When exposed to low or let radiation, changes in gastrointestinal (GI) microflora may occur, and these changes may disturb the important relationship between gastrointestinal microflora and human health. In future transformation research, using precision medicine methods, it is possible not only to identify relevant exposure and action mechanisms, but also to stimulate intelligence and improve the diagnosis of treatment results [60,61].

The brain gut microbiota axis is a bidirectional communication system enabling gut microbes to communicate with the brain and the brain with the gut [62]. Preclinical studies have implicated the vagus nerve as a key route of neural communication between microbes of the gut and centrally mediated behavioral effects [63]. This communication is mediated by several microbially derived molecules that include short chain fatty acids (SCFAs), secondary bile acids (2BAs), and tryptophan metabolites. These molecules propagate signals primarily through interaction with enteroendocrine cells (EECs), enterochromaffin cells (ECCs), and the mucosal immune system, but some cross the intestinal barrier, enter systemic circulation, and may cross the blood brain barrier. The gut microbiota also regulates key central neurotransmitters, such as serotonin, by altering levels of precursors [64,65]. Lactobacillus and Bifidobacterium spp can produce g-aminobutyric acid (GABA); Escherichia, Bacillus, and Saccharomyces spp can produce noradrenaline; Candida, Streptococcus, Escherichia, and Enterococcus spp can produce serotonin; Bacillus can produce dopamine; and Lactobacillus can produce acetylcholine. These microbially synthesized neurotransmitters can cross the mucosal layer of the intestines, it is impact on brain function is likely to be indirect, acting on the enteric nervous system [66,67]. SCFAs, which include butyrate, propionate, and acetate, are essential metabolic products of gut microbial activity and may exert central effects either through G-protein–coupled receptors, although such receptors are sparsely concentrated in the brain. It is more likely that they act as epigenetic modulators through histone deacetylases. SCFAs are also involved in energy balance and metabolism and can modulate adipose tissue, liver tissue, and skeletal muscle and function [68]. Immune signaling from gut to brain mediated by cytokine molecules is another documented route of communication. Cytokines produced at the level of the gut can travel via the bloodstream to the brain. Increasing evidence indicates a capacity to signal across the BBB and to influence brain areas [69]. It is through the mechanism the cytokines interleukin (IL)-1 and IL-6 activate the hypothalamic-pituitaryadrenal (HPA) axis, bringing about the release of cortisol. This is the most potent activator of the stress system. The HPA axis, which provides the core regulation of the stress response, can have a significant impact on the brain gut microbiota axis. It is increasingly clear and probably of relevance in several pathologic conditions that psychological or physical stress can significantly dysregulate the HPA axis and subsequently the brain gutmicrobiota axis [70].

In recent years, the brain gut axis is involved in the development of various human diseases; however, related research is still very limited. Moreover, the research related to the brain gut axis has been widely used in the diagnosis and prognosis treatment of many diseases, and the study of the brain gut axis in encephalopathy has become a new research direction for scientific researchers [71,72]. With the pathogenesis of irritable bowel syndrome in the brain intestinal axis flora regulation treatment of more attention, it can be seen that exploring the mechanism of brain gut axis has been the mainstream of research, the action of brain gut axis, intestinal mechanism, microbes in the intestinal flora brain axis and its application in irritable bowel syndrome is the research hotspot and newly arisen research direction. With the deepening of the brain gut axis research, it is believed that there will be more hot spots in the near future, especially referring to the role of the brain gut axis in the treatment of human diseases [73-83].

## Conclusion

In conclusion, the research on brain gut axis is in the stage of rapid development. Annual publications on brain gut axis have been published continuously since 2012, especially in the past two years, and the number of publications has increased rapidly. The most common categories associated with the brain gut axis are molecular psychiatry and neurology. China has made great contributions in this field, while the United States has also played a major role and has a high central position. Because the brain gut axis is a newly discovered two way pathway, most of the keywords that appear most frequently in the field of brain gut axis are related to the mechanism or pathway of brain gut axis. "Irritable bowel syndrome" is the strongest term of citation outbreak, and "exposure" is the latest outbreak term in recent years. With more and more evidence that brain gut axis plays a role in the pathogenesis of many diseases, it may soon become a new hot spot worthy of close attention in the treatment of gastrointestinal and nervous system diseases. Similarly, because the collection of literature in this study is limited to a single database and the way of literature retrieval may cause the omission of individual data, the analysis of this field may be limited. In general, compared with traditional research, we believe that the results of this study will provide objective insights for further research.

## Funding

This work was supported by the National Natural Science Foundation of China (81874453), the Natural Science Foundation of Guangxi Province, China (2020GXNSFAA297270). The funding source had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Conflicts of Interest

The authors declare no conflicts of interest, financial, or otherwise.

## Authors Ethical Approval

This paper has been approved by the ethical review board of the Guangxi University of Chinese Medicine.

## Contributions

W.M., X.M.conceived of the study and revised the manuscript for important intellectual content. Y.B., TX and Y.Z. performed the literature search and contributed all the figures. Q.X.Z.G. edited the manuscript.

## Informed Consent

All authors have read and approved the content of the manuscript.

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**How to cite this article:** Mo, Xue Ni, Yi Bao Y, Ting TX and Wei M, et al. "An Analysis of Global Research Hotspots and Trends on Gut Brain Axis with Web-Based Scientific Database" *J Neurol Disord* 10 (2022):508.